“Studies on Synthesis and Characterization of Nitrogen Heterocycles as Metal Chelates and Their Biological Investigations”

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SYNOPSIS

"STUDIES ON SYNTHESIS AND CHARACTERIZATION OF NITROGEN HETEROCYCLES AS METAL CHELATES AND THEIR BIOLOGICAL INVESTIGATIONS."

Introduction:

The history of heterocyclic chemistry began in the 1800s, in step with the development of organic chemistry. Nitrogen heterocycles are central to the chemical reactions that occur in all organisms. The metabolic transformations of amino acids into five, six and seven membered heterocycles reveal the chemical logic and enzymatic machinery for shutting primary metabolites into bioactive heterocyclic nitrogen scaffolds.[1]

More specifically nitrogen heterocycles are abundant in nature existing as part of vitamins, hormones, antibiotics, and alkaloids.[2] Heterocycles are class of compounds especially relevant in the life in the life processes through their enzymatic functions and the hereditary information transfer.[3] They also find applications in medicine, agriculture, industry and in different areas of chemistry and bio-chemistry.[4] Heterocycles are known to govern many crucial processes inside our body such as provision of energy, transmission of nerve impulses, sight, metabolism, transfer of hereditary information, etc., are performed by heterocyclic compounds like vitamins, enzymes, coenzymes, ATP, DNA, RNA and serotonin.[5]

Heterocyclic bridging ligands with two adjacent nitrogen donor atoms has gained more attention because they are capable of positioning two metal centres in close proximity such that they interact magnetically and electronically, give rise to novel properties and reactivities.[6] Pyrazole is such an interesting and important nitrogen heterocycle due to its 1,2- diazine unit which can provide the endogenous bridging between two similar and dissimilar metal ions.[7] In the literature pyrazole derivatives are well established as important biologically active heterocyclic compound. These derivatives are the subject of many research studies due to their widespread potential biological activities such as anti- inflammatory[8], antipyretic[9], antimicrobial[10], antiviral[11], antitumor[12], anticonvulsant13, antihistaminic, antidepressant, insecticides and fungicides.[14]

The application of pyrazolate moiety as a bridging unit of ligand system has gained considerable attention as it can hold the two metal centres in a close proximity.[15] Due to which, the complexes derived from such type of ligand system acts as the origin for the versatile behaviour of metal complexes. The

ligands derived from pyrazole or heterocyclic systems have been widely applied in the fields of catalysis, biochemistry, and medicine.[16] Heterocyclic ring systems compounds have been more and more attention in the recent years because they are proven to be extremely useful intermediates for the synthesis of new biologically active compounds.[17] Pyrazole and its derivatives are important five membered heterocyclic compounds containing two adjacent nitrogen as hetero atoms. Therefore they are useful scaffolds in drug designing research as well as are extensively useful synthons in organic chemistry.

The another nitrogen containing heterocyclic compound thiazole molecule have attracted significant interest and gained special attention not only in structural chemistry of their multifunctional coordination modes but also showed importance in medicinal and pharmaceutical fields.[19] This is because thiazole have a great pharmacological activity. Many thiazole derivatives such as – sulphathiazole, ritonavir, abafungin, blemycim and tiazofurine are well known as potent biologically active compounds.[20] Moreover, thiazoles are very important building blocks in medicinal chemistry and can be found in numerous natural products and biologically active compounds including antimicrobial, anti- inflammatory, antihypertensive, anti-HIV, anticancer, and cytotoxic activity that can be well illustrated by large number of drugs in the market containing the moiety.[21]

Thiazole and pyrazole rings are also found applications in polymer, liquid crystal, photo nucleases, fluorescent dyes, insecticides and antioxidants.[22] Their transition metal complexes have attracted deal of interest with DNA molecules.[23] The complexes that can bind or cleave DNA molecule at exact sites, play an important role in genomic investigation and in photodynamic therapy against cancer.[24]

The multi functionalized quinolines as a pharmacophore imitates a class of heterocyclic compounds with compelling pharmacological proficiency, engrossing antiviral, antimalerial, antiasthmatic, anti-inflammatory, antibacterial, antifungal and anticancer.[25]

Pyrimidines and condensed pyrimidines are also received much attention over the years because of their interesting pharmacological properties.[26] Pyrimidines are well known for their pharmacological, anticancer, antimicrobial, antioxidant and antiviral activities.[27] Nitrogen heterocyclic compounds and their derivatives have attracted great attention due to their widespread applications in pharmaceutical and in agrochemical industries. One of the most important nitrogen heterocycle, called pyrazole as the central core in the biologically active molecule has grown rapidly in the past decade.[28]

The number of nitrogen heterocyclic derivatives and their metal chelates were also reported to have promising bioactivities including anticancer[29], antimicrobial, anti-inflammatory[30], antihypertensive, antifungal, anti-amoebic, antiviral, antitumor, antidepressant, insecticides, and anti histamic[31], analgesic, cytotoxic, antidiabetic, and anticoagulant.

2) Research Problem: The theme of proposed research work is synthesis of different nitrogen heterocyclic derivatives as metal chelates because they have fundamental applications in various fields such as in medicine, agriculture, biological, industrial, biochemistry, natural product synthesis, polymer, material science, fluorescent dyes and as insecticides.[32]

Recently in a day today life the scientists are trying to synthesize novel bioactive heterocyclic compounds which are beneficial for society. In the recent days nitrogen heterocyclic metal chelates also plays important role for variety ofdiseases.[33]

Prompting these various medicinal, pharmacological, agricultural, industrial, etc., applications of nitrogen heterocyclic compounds such as pyrazole, thiazole, pyrimidines and quinoline nucleus has gathered considerable attention due to their biological activities and industrial significance.

In this sense, the studies concerning the synthesis, characterization and applications of nitrogen heterocycles and their metal chelates constitute an important issue.

3) International Significance of Research Work :

Cancer is enduring to be a major health issue in developing as well as underdeveloped countries.[34] Breast cancer is the most persistent cancer worldwide and the second leading cause cancer related death among females in

the world. The global concern of breast cancer exceeds all the other cancers and the incidence rate of breast cancer are increasing.[35] Breast cancer is a malignant tumour is a cluster of cancer cells that be capable to grow into (invade) surrounding tissues to other distant areas of the body.[36] For this reason, there is a sustaining concern regarding the development of new and advantageous anti- breast cancer drugs.

Tuberculosis (TB) is a terribly infectious epidemic induced by the pathogenic bacterium Mycobacterium tuberculosis. WHO report implies that TB is one of the worlds lethal contagious disease.[37] It projected that there were 9.0 million unique cases in 2013 and that up to 2020 nearly one billion people might be infected and over 30 million may die due to TB.[37]

Recently, several reports have appeared in the literature describing the anticancer activity of Cu(II) complexes of many classes of nitrogen donors including thiosemicarbazone and imidazole. Specially pyrazole containing complexes have been reported to possess antitumor activity which is comparableto that of Cisplatin.[38]

Alzheimer's disease is the most common type of dementia disease in society. This disease is characterised by oxidative stress, misfolded proteins, neuronal cell loss and eventually death.[39] The ligand 8- hydroxyquinoline and their derivatives form complexes with Cu(II) which inhibit peptide aggregation. Cu(II),Zn(II),and Fe(II) exhibit a relatively high binding affinity with α, β peptides and induce the formation of toxic oligomer's and reactive oxygen species leading to oxidative stress.[40]

A large body of evidences indicates that the pyrazole derivatives and their metal chelates exhibit biological activity by binding to DNA of affecting cells and inhibiting the replication.[41] For example, the 3,5 and 4,5–disubstituted-1H- pyrazole derivatives and their metal chelates of transition metals are found to be capable to selective interactions with DNA double helix.[42]

The treatment of infectious diseases always remains a significant and serious problem in the society, because of increasing number of multidrug resistant microbial pathogens and combination factor's including emerging infectious diseases. The increasing human resistance, antimicrobial agents are being well thought-out as essential sources in novel drug discoveries for treating a range of fungal and bacterial infections.

The ligands of nitrogen heterocycles such as – pyrolidione and pyridine derivatives form metal complexes with Cu(II) which shows antibacterial activities. The potential significance of various nitrogen heterocyclic ligands and

their metal chelates growing interest in scientific community and motivated to opportunity for many research work.

Given the background and motivation, I would like to focus on nitrogen heterocyclic derivatives and their metal complexes have great significance in various fields.

5) Brief Review of Literature:

After Literature survey to the best of our knowledge showed thattremendous work based on synthesis and preparation of metal chelates of nitrogen containing heterocyclic compounds yet to explore. Pyrazolo pyrimidine derivatives were also reported to have biological properties including inhibitor's, anticancer, antibacterial, and antiviral activities. Thiazolo pyrimidine derivatives which can be considered as thia-analogues of the natural purine bases such as adenine and guanidine, have acquired a growing importance as anticancer,antitumor and antibacterial agents.

In addition, nitrogen heterocyclic Schiff bases of pyrazole, thiazole, pyrimidine and quinoline are able to inhibit the growth of several types of tumors and their metal chelates have shown good antibacterial, anti- inflammatory, antiviral, alkaloids, rubber chemicals and flavouring agents.[43]

Some review deals with the synthesis and biological activity of pyrazolo quinazoline derivatives have been used successfully for the production of biologically

important compounds. Synthesis of novel series of 1-(chlorophenyl)-4- hydroxy-1H-pyrazoles counterparts through a carbonyl bridge are biologically active nitrogenous heterocycles by an amide linker were selected by the National Cancer Institute (NIC) in vitro disease oriented antitumor agents.

Tetrahydroquinoline scaffold is deliberated as one of the privileged structure in the field of drug discovery as vast range of biological and pharmaceutical activities.[44]

Out of limitless heterocyclic compounds thiazole and pyrazole pharmacophores are of gaining prime interest in medicinal and organic chemistry. Pyrazoles are well established as one of the foremost heterocyclic units, which have been extensively used as relevant building block for pharmaceutical agents. The pyrazole and their derivatives are enriched with many biological and pharmacological properties such as antimicrobial[45],anti-inflammatory[46], antidepressant[47], antiviral and antitumor.[48] In addition many thiazole derivatives imparting wide range of biological activities like antitubercular, antifungal, analgesic and anticancer[49], antimicrobial[50], and anti-inflammatory activity.[51]

Some review shows that, tetrazole bearing heterocyclic compound investigated extensively due to their unique structure and wide range of biological applications as antibacterial, antifungal, analgesic, anti-inflammatory, anti convusant, antitubercular, anticancer, antidiabetic, antihypertensive, antiviral and antiulcer.[52] The drug which is available in market known as Sulfonamide (Sulfa drug) is the prior effective treatment to be employed progressively for the prevention and curing of microbial infections.

Pyrazolopyrimidines and related fused heterocycles are of gaining enough concern as potential bioactive molecules. It is a facile scaffold for the synthesis of potential drugs. They also possess wide applications in the field of medicine, and agriculture. They exhibit diversified pharmacological activities like antibacterial, antifungal, CNS-depressant, antiviral, anticancer and tuberculostatic.[53]

After the review of various methods for the synthesis of nitrogen heterocyclic derivatives as metal chelates and their applications, it was found that they have very much attention of international and national researchers.

5) Objectives of Research Study:

The objective of research is an increasing interest in designing and synthesis of nitrogen containing heterocyclic derivatives as metal chelates and their metal complexes. The development of novel pharmaceutically active agents is a convincing and challenging task for medicinal chemistry. Many research programs are assigned towards design and synthesis of new bioactive drugs.

Nitrogen containing heterocycles form a fundamental core of several pharmacophores and occupy an obvious position in medicinal chemistry. They demonstrate diverse biological and pharmacological activities and resemblance with many natural and synthetic molecules with known biological activity. Keeping in

mind the objective of research will be synthesis of various substituted nitrogen heterocycles and to investigate their applications in different fields.

6) Outline of the proposed Research Work:

The proposed research work will be completed in four phases.

Phase -I :-

In first phase, the extensive collection of references, along with literature survey, synthesis of starting materials, intermediate compounds and purification of solvent will be done.

Phase -II:

In second phase the maximum attention will paid on the synthesis and characterization and biological activities of nitrogen containing heterocycles which acts as metal chelates.

Phase-III:-

The third phase covers the synthesis and characterization of metal chelates on the basis of techniques such as IR, ^{1}H NMR, ^{13}C NMR, Mass and X-ray crystallography etc.

Phase IV:-

In this phase the biological applications of synthesized metal chelates will be investigated and research work will be published in reputed research journals.

The work carried out under these schemes will be submitted in the form ofthesis for the award of Ph. D. degree in chemistry.

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